## REMARKS

This document is filed in response to the final Office Action dated December 18, 2006 ("final Office Action") and the Advisory Action dated April 23, 2007 ("Advisory Action").

Applicants have amended claims 1 and 20 to remove non-elected subject matter. These amendments have necessitated cancellation of claims 3, 6, and 21. Applicants have further amended claim 20 to replace "adverse reactions" with "Steven-Johnson syndrome or toxic epidermal necrolysis in response to carbamazepine." Support for this amendment can be found at, e.g., in original claims 2 and 5. Finally, Applicants have narrowed claims 1 and 20 to "the patient is a Mongoloid or a Mongoloid descendent," which is supported by the specification. See discussion immediately below.

Upon entry of the amendments, claims 1, 8-12, 20, and 22-25 will be under examination. Applicants respectfully request that the Examiner reconsider this application.

Support for "a Mongoloid or Mongoloid descendent"

Applicants have incorporated in claims 1 and 20 the phrase "a Mongoloid or Mongoloid descendent." For the reasons set forth below, Applicants submit that the specification supports this amendment.

Whether a phrase recited in a claim is supported by the specification shall be determined based on what the specification is reasonably communicated to those skilled in the art. See MPEP § 2163.05, citing *In re Wilder*, 222 USPQ 369, 372 (Fed. Cir., 1984). Indeed, the phrase at issue does not have to be set forth verbatim in the specification. In *In re Wright*, 9 USPQ2d 1649 (Fed. Cir. 1989), the Federal Circuit, in reversing a Board's 35 U.S.C. § 112, first paragraph rejection, held that there was adequate written description support for applicant's claim limitation, despite the fact that it was not set forth "*in haec verba*" (i.e., "in these words" or "verbatim") in the specification.

The present specification discloses that the genetic background of patients recruited in Taiwan is associated with the development of adverse drug reactions. See page 28, lines 6-15. As these patients' genetic backgrounds are pertinent, a skilled person would readily pay attention

to their races. Note that a race is "a major living subspecies of man differentiated by genetic and physical characteristics," according to Medical Subject Headings (MeSH). See *Nature Genetics*, 34:119-120, 2003 (copy attached as Exhibit 1). MeSH lists four major racial groups among humans: Caucasoid, Mongoloid, Negroid, and Australoid. See Exhibit 1, page 119. It further defines Mongoloids as "individuals whose ancestral origins are in the continent of Asia." See Exhibit 2. Based on these teachings, a skilled artisan would know that the patients recruited in Taiwan are Mongoloids or Mongoloid descendents as Taiwan is just 60 miles away from the continent of Asia. In other words, he or she would know that each of the patients recruited in Taiwan is "a Mongoloid or Mongoloid descendent." Following *Wilder* and *Wright*, the present specification clearly supports the phrase "a Mongoloid or Mongoloid descendent," even though it does not literally recite it.

In view of the above remarks, Applicants respectfully request that the Examiner allow entry of this amendment.

Claim Objections

Claims 1, 12, and 20 are objected to for reciting subject matter that is not elected. See the final Office Action, pages 2-3, section 1. Applicants have deleted the non-elected subject matter from claims 1 and 20. Applicants, however, disagree that non-elected species should be removed from claim 12. Please note that claim 12 recites a Markush group that includes six species of equivalent genetic marker of HLA-B*1502, e.g., the elected species HLA-Cw*0801. MPEP § 803.02 requires that the patentability of the elected species be examined first and if it is found allowable, the examination should be extended to the non-elected species. Applicants thus submit that it is not necessary to remove the non-elected species from claim 12 at this point.

Claim Rejection under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 1, 3, 6, 8-12, and 20-25 stand rejected for lack of enablement on four grounds. Among the rejected claims, claims 3, 6, and 21 have been cancelled. Applicants will traverse each of the grounds below.

I

Apparently referring to claims 20-25, the Examiner asserts that the specification does not "reasonably provide enablement for assessing the risk of **any** other adverse reactions in response to **any** other drugs." See the Office Action, page 3, third paragraph; emphases added. Note that claim 21 has been cancelled.

Applicants have amended claim 20 to limit it to only one adverse drug reaction, i.e., Stevens-Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN), and only one drug, i.e., carbamazepone (CBZ). It is submitted that the amendments have rendered moot the Examiner's ground for rejecting claim 20, as well as claims 22-25 dependent from it.

II

The Examiner asserts that the specification is not enabling for assessing the risk of adverse drug reactions in any human population. See the final Office Action, page 3, third paragraph; and the Advisory Action, page 2, second paragraph.

Applicants have narrowed independent claims 1 and 20 to "a Mongoloid or Mongoloid descendent." In other words, these two claims, as amended, no longer encompass "any human population" and are enabled by the specification.

III

Referring to claim 11, the Examiner alleges that "[i]t is unpredictable as to whether or not the presence of any equivalent genetic marker is useful for determining the presence of the HLA-B*1502 allele or for the assessment of risk of drug adverse reaction." See the Office Action, page 8, second paragraph. Applicants disagree.

The specification defines an "equivalent genetic marker" of an allele of interest as "a genetic marker that is linked to the allele of interest." See page 8, lines 19-20. It further states that "[t]he useful equivalent genetic markers in the present invention display a linkage disequilibrium with the allele of interest." See page 8, lines 20-21. Based on these teachings, one skilled person in the art would know that the presence of an equivalent genetic marker of HLA-B*1502 indicates the presence of this HLA allele. Thus, he or she would recognize that

any equivalent genetic marker, as recited in claim 11, could be useful for determining the presence of HLA-B*1502 and thus for assessing the risk of developing CBZ-induced SJS/TEN.

For the above reasons, Applicants respectfully request that the Examiner withdraw this rejection.

IV

Finally, referring to claim 12, the Examiner asserts that "there is no statistical analysis of the significance of the association of HLA-Cw*0801 with carbamazepine-induced SJS/TEN, nor any analysis of the linkage of HLA-B*1502 with HLA-Cw*0801." See the Office Action, page 8, second paragraph. Applicants disagree.

It is well known in the art that HLA-B*1502 has a strong linkage disequilibrium with HLA-Cw*0801. See Romphruk et al., *European J. Immunogenet.*, 30:153-158 (2003), page 4, Table 4 and right column, second paragraph; and Romphruk et al., *Tissue Antigens*, 58:83-89 (2001), page 86, Table 4, and page 87, left column, first paragraph (copy of both articles submitted herewith as Exhibits 3 and 4). Further, the Specification teaches that 38 of 42 carbamazepine-induced SJS/TEN patients (HLA-B*1502 carriers) have HLA-Cw*0801 allele. In other words, as many as 90% (38/42) of the SJS/TEN patients carry HLA-Cw*0801. As the association between HLA-Cw*0801 and CBZ-induced SJS/TEN (90%) is clearly significant, one skilled person in the art would readily recognize that HLA-Cw*0801, an allele co-present with HLA-B*1502, is an indicator of the risk of developing CBZ-induced SJS/TEN in a patient. Indeed, this conclusion is supported by a post-filing reference, Hung et al., which shows that 56 out of 60 SJS/TEN patients carry HLA-Cw*0801. See Hung et al., Pharmacogenetics and Genomics, 16(4):297-306 (2006), a copy of which is submitted herewith as Exhibit 5.

For the reasons set forth above, Applicants submit that the specification is enabling for claim 12, which recites HLA-Cw*0801. It is thus respectfully requested that the Examiner withdraw this rejection.

## CONCLUSION

It is believed that all of the pending claims have been addressed. However, the absence of a reply to a specific rejection, issue or comment does not signify agreement with or concession of that rejection, issue or comment. In addition, because the arguments made above may not be exhaustive, there may be reasons for patentability of any or all pending claims (or other claims) that have not been expressed. Finally, nothing in this paper should be construed as an intent to concede any issue with regard to any claim, except as specifically stated in this paper, and the amendment of any claim does not necessarily signify concession of unpatentability of the claim prior to its amendment.

The Petition for Extension of Time fee in the amount of $1,020 is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to Deposit Account No. 50-4189, referencing Attorney Docket No. 70003-003001.

Respectfully submitted,

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